



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,724	03/06/2002	Samy Ashkar	CMCC 820	6946

9629 7590 01/12/2005
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER

MYERS, CARLA J

ART UNIT PAPER NUMBER

1634

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/091,724	Applicant(s) ASHKAR, SAMY	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 and 23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 March 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>8/6/02; 7/22/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on November 1, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that in the response of November 1, 2004, Applicants state that the requirement to elect a single species with respect to Group I has been obviated by the cancellation of claims 19-22. This statement is correct. Accordingly, claims 1-18 and 23 have been examined herein. Claims 19-22 and 24-44 have been cancelled.

Claim Objections

2. Claim 13 is objected to because of the following informalities:

In claim 13, "*Rickettsia rickettsii*" should read "*Rickettsia rickettsii*."

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-11 are indefinite over the recitation of "the minicell strain" because this phrase lacks proper antecedent basis. While the claims previously refer to a "minicell host," the claims do not previously refer to a "minicell strain."

Claims 9 and 12 are indefinite over the recitation of "selected from the group comprising" because the claim recites an improper format for a Markush group. Claims which recite members of a Markush group must be "close-ended". This rejection may be overcome by amendment of the claim to recite "group consisting of". See MPEP 2173.05(h).

Claim 12 is indefinite over the recitation of "the DNA encoding the fusion protein" because this phrase lacks proper antecedent basis. While the claim previously refers to a 'chimeric gene' comprising DNA fragments encoding a first and second peptide, the claim does not previously refer to a DNA encoding a fusion protein.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-10, 12, 14-18 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (U.S. Patent No. 5,516,637; cited in the IDS) in view of Clark-Curtiss (Methods in Enzymology (1983) 101: 347-362).

Huang teaches methods for identifying host cells bound to a binding partner and methods for synthesizing, detecting and characterizing a fusion protein wherein the methods comprise: (i) expressing a fusion protein in a host cell wherein the fusion protein is encoded by a chimeric gene comprising a first DNA fragment encoding a first peptide that mediates attachment of the fusion protein to the outer membrane and a

Art Unit: 1634

second DNA fragment encoding a second target peptide; (ii) contacting the host cell with a binding partner so as to form a complex between the fusion protein/host cell and the binding partner and detecting the host cells bound to the binding partner (see columns 5-7). In particular, Huang teaches that the first DNA fragment encodes for a protein that includes a signal sequence that allows for the fusion protein to be expressed and displayed on the cell surface (column 6). Preferably, the first DNA fragment includes the signal sequence of the TraA gene (column 6). Huang (column 6) further teaches that the second DNA fragment encodes for a peptide capable of forming a complex with a binding partner, wherein the binding partner may be a peptide, protein, receptor, ligand or enzyme. Additionally, Huang teaches that the fusion protein/host cell/binding partner complex may be isolated and separated from unbound material by affinity separation techniques (see, e.g., column 8, lines 43-61). Huang teaches performing the method using bacteria host cells to express the fusion protein, but does not teach using bacterial minicell hosts to express the fusion protein.

However, Clark-Curtiss teaches methods for expressing heterologous proteins present in a plasmid using minicell hosts. The reference teaches methods of making minicells and teaches that *E. coli*, *Vibrio*, *Erwinia* and *Bacillus* have been used to express heterologous proteins from plasmids (e.g., page 347). Clark-Curtiss teaches that minicells are produced continually during growth of the bacterial culture and contain RNA and protein, but little or no chromosomal DNA. Consequently, while recombinant proteins synthesized in bacterial cells are often unstable due to proteolytic degradation, proteins expressed by minicells may be more stable (see, e.g., page 351 and 361).

Art Unit: 1634

Additionally, the reference teaches that minicells can be used to assay for proteins expressed and displayed on the outer membrane of minicells (page 361).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Huang so as to have used bacterial minicells in place of bacterial cells to express the fusion protein. The ordinary artisan would have recognized that synthesis of the fusion protein in minicells would have ensured a higher stability of the fusion protein and would have enhanced the specificity of the detection of the fusion protein because minicells are not subject to the high background of chromosomal gene products which occurs when using bacterial cells. Accordingly, one of ordinary skill in the art would have been motivated to have used minicells in the method of Huang in order to have provided a more sensitive and accurate means for detecting fusion proteins having target peptides which bind to a binding partner.

With respect to claim 5, Huang teaches that the second DNA fragment encodes for a peptide from a DNA library (see column 9). With respect to claim 12, Huang teaches that hosts harboring the selected fusion protein may be isolated, and the DNA encoding the fusion protein separated and further characterized by sequencing or affinity analysis (see, e.g., column 9, lines 20-23 and column 12). With respect to claims 14 and 15, Huang teaches that expression of the fusion protein is controlled by an inducible promoter element, such as lac (see, e.g., Figure 1, column 7 lines 66-67 to column 8 line 9; and column 8, lines 22-25).

With respect to claims 16-18, Huang states that "The fusion protein can be detached from selected cells. If desired, the target protein may be separated from the pilin protein and further purified" (see column 2, lines 46-48). Huang also teaches that the target peptide (i.e., the second peptide) may be cleaved from the fusion protein with a protease and monitored by SDS-PAGE or by examining other properties of the peptide (see column 7, lines 22-27). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have separated the second peptide from the minicell by cleavage and to have analyzed the second peptide using techniques known in the art, such as SDS-PAGE to determine the molecular weight of the peptide, in order to have further characterized the structural properties of the isolated peptide.

5. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huang in view of Clark-Curtiss, as applied to claims 1-10, 12, 14-18 and 23 above, and further in view of Shivakumar et al. (Plasmid. 1979. 2: 279-289).

The teachings of Huang and Clark-Curtiss are presented above. In particular, Clark-Curtiss teaches that minicells may be obtained from *Bacillus* (page 347), but does not specifically teach minicells from *Bacillus subtilis*.

However, Shivakumar (see abstract and page 286) teaches transformation of *B. subtilis* minicells with plasmids and use of the transformed minicells to express recombinant polypeptides. Shivakumar also teaches that *B. subtilis* minicells are free of chromosomal DNA and are useful for study gene expression of cloned DNA fragments.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have specifically used *B. subtilis* minicells to express the fusion protein in the method of Huang because, as taught by Shivakumar, *B. subtilis* minicells provide an effective host for synthesizing recombinant polypeptides and use of *B. subtilis* minicells in the method of Huang would have provided an equally effective means for synthesizing the fusion polypeptide, while avoiding the problems of proteolytic cleavage and background chromosomal encoded proteins which occur when using nucleated bacterial cells to synthesize plasmid encoded polypeptides.

6. Claims 4 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang in view of Clark-Curtiss, as applied to claims 1-10, 12, 14-18 and 23 above, and further in view of Georgiou (U.S. Patent No. 5,348,867).

The teachings of Huang and Clark-Curtiss are presented above. In particular, Huang teaches that the first DNA fragment contains a signal sequence that directs the encoded peptide to the cell membrane, but does not teach that the DNA fragment encodes a signal sequence encoding the 17K antigen of *Rickettsia rickettsii*.

Georgiou (see, e.g., column 3) teaches methods for synthesizing fusion proteins that are expressed on a host cell's surface. Georgiou teaches chimeric genes containing a first DNA fragment encoding a signal sequence that directs a fusion protein to be expressed and anchored to the outer membrane of the host cell. The reference teaches a number of signal sequences that may be used for this purpose and specifically teaches that the signal sequence may be obtained from the 17kDa

Art Unit: 1634

lipoprotein from *Rickettsia rickettsii* (column 3, lines 53-68 through column 4, line 3; column 5, lines 29-56).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Huang so as to have used the signal sequence from the gene encoding the 17KDa lipoprotein of *Rickettsia rickettsii* in place of the signal sequence from the TraA gene because this would have provided an equally effective signal sequence for targeting and anchoring the fusion protein to the host cell outer membrane.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Puente teaches methods for expressing proteins in minicells and specifically teaches expressing the ompC outer membrane protein in *E. coli* minicells. In the method of Puente, the ompC pore protein is effectively expressed and inserted into the membrane of *E. coli* minicells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Art Unit: 1634

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
January 3, 2005


CARLA J. MYERS
PRIMARY EXAMINER